REMARKS

Claims 1-18 and 21-29 are currently pending in this application. According to the Office Action mailed on November 5, 2007, claims 1-20 have been examined on their merits and have been objected to and/or rejected. Claims 21-27 have been withdrawn as directed to non-elected subject matter.

This Amendment amends claims 1, 7 and 13, cancels claims 19 and 20, and adds new claims 28 and 29. These amendments are made without prejudice to filing one or more continuation or divisional application to the deleted subject matter. No new matter has been added to the application by the above amendments. As discussed below, the amendments to the claims and the new claims are fully supported by the specification. In view of the amendments to the claims and the remarks below, Applicants respectfully request that the objections and rejections asserted in the Office Action be reconsidered and withdrawn.

Claims 1, 7 and 13 have been amended to recite a method comprising the steps of "identifying at least one 4G allele and/or genotype at the plasminogen activator inhibitor-1 (PAI-1) gene promoter site in the human subject, and advising the subject to engage in exercise training for a period of time sufficient to decrease the level of tissue plasminogen activator (t-PA) antigen". Support for this amendment is found in the specification, for example, at paragraph [0047] (Table 1). Table 1 shows that t-PA antigen levels are significantly reduced in subjects who had one 4G allele after the subject had engaged in exercise training. Therefore, the specification supports claims directed to identifying subjects having at least one 4G allele, and advising exercise training to decrease the level of (t-PA).

New claims 28 and 29 are supported by the specification. These claims are directed to a method comprising the steps of "identifying two 4G alleles and/or genotype at the plasminogen activator inhibitor-1 (PAI-1) gene promoter site in the human subject, and advising the human subject to engage in exercise training for a period of time sufficient to increase the level of (t-PA) activity". Support for these new claims is found in the specification, for example, at paragraph [0047] (Table 1). Table 1 shows that (t-PA) activity levels are significantly increased after individuals having two 4G alleles have engaged in exercise training. Furthermore, the specification establishes that increased (t-PA) activity increases fibrinolysis and consequently can ameliorate cardiovascular disease (see, for example, paragraphs [0004], [0007], [0012] and [0050].

Objection to the Claims

Claims 1, 7 and 13 have been objected to for recitation of "subject", "PAl-1", and "at least one 1 allele". Claims 1, 7 and 13 have been amended so that "subject" now recites "human subject", and "PAl-1" recites "PAI-1". The phrase "at least one 1 allele" has been deleted from the claims. Accordingly, Applicants respectfully request that these objections be reconsidered and withdrawn.

Rejection under 35 U.S.C. §132(a)

The specification has been objected to under 35 U.S.C. §132(a) because the amendment to paragraph [0021] purportedly introduced new matter into the application. Particularly, the Office Action contends that paragraph [0021] originally defined "limited exercise" to include about 5 single courses of exercise, but the amendment to paragraph [0021], which recited "less than about 5 single courses of exercise", does not include 5 single courses of exercise. To expedite examination of the application, Applicants have amended paragraph [0021] to recite "less than or equal to about 5 single courses of exercise, without prejudice". Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejection under 35 U.S.C. §112, First Paragraph

Claims 1, 7 and 13 have been rejected under 35 U.S.C. §112, first paragraph as purportedly failing to comply with the written description requirement. On pages 5-6, the Office Action contends that "the specification does not specifically contemplate the use of PAI genotype **in combination with** t-PA genotype in an individual as indicative of increased fibrinolysis". While Applicants respectfully disagree with the rejection, the claims, as amended without prejudice, are directed to identifying a person with at least one PAI-1 4G allele, and no longer recite additionally identifying a person with an t-PA I allele. Therefore, the claims are not directed to the use of PAI genotype in combination with t-PA genotype. For this reason, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Claims 6, 12 and 18 have been rejected under 35 U.S.C. §112, first paragraph, as purportedly failing to comply with the written description requirement. On pages 6-7, the Office Action contends that "the claims of the instant application are drawn to a method of increasing fibrinolysis in a subject comprising engaging a subject in 'limited exercise'". It is believed that the basis of this rejection was the amendment to the specification regarding the

definition of "limited exercise". As discussed above, the definition of "limited exercise" has been amended to include about 5 single courses of exercise. For this reason, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Claims 1-20 have been rejected under 35 U.S.C. §112, first paragraph, as purportedly failing to comply with the enablement requirement. For brevity, reference is made to the Office Action at pages 7-14 for the complete reasons for rejection. At page 9, the Office Action contends that "while the specification asserts that there is a tendency for subjects with 4G/4G genotypes to respond better than subjects with 4G/5G or 5G/5G genotypes (paragraph [0048]), the analysis of the data (P ANOVA) indicates that none of the changes are statistically significant".

Applicants respectfully traverse this rejection and disagree with this contention because, as evidenced by Kulaputana et al. (Genetic Markers of Fibrinolytic Responses of Older Persons to Exercise Training, Int'l J. of Sports Med. (2006) 27: 617-622), the data in Table 1 contains statistically significant data. A copy of the Kulaputana et al. article is submitted with this amendment.

The Kulaputana et al. article, authored by the inventors among others, discusses the same experiments and reports the same data as set forth in Example 6 of the present application. Table 2 in the article corresponds to the data reported in Table 1 of this application. Likewise, Table 3 in the article corresponds to the data reported in Table 2 of this application.

The Kulaputana et al. article discloses that statistically significant changes in (t-PA) antigens after exercise were observed when the test subject had at least one PAI-1 4G allele. The article reports that for individuals genotyped as 4G/4G, there was a -1.0 ± 0.3 changes in (t-PA) antigen levels after the subjects exercised. This change is reported as statistically significant because it has a p-value of less than 0.01. The article reports that, for individuals genotyped as 4G/5G, there was a -0.9 ± 0.3 change in (t-PA) antigen levels. This change is also reported as statistically significant because it has a p-value of less than 0.05. Therefore, the article evidences that there are statistically significant changes in (t-PA) antigen levels in individuals, carrying at least one PAI-1 4G allele who exercise. Claims 1-18 relate to this statistically significant change in (t-PA) antigen levels when a person having at least one PAI-1 4G allele exercises.

The Kulaputana et al. article also discloses that the inventors observed statistically significant changes in (t-PA) activity when a subject was homozygous for the PAI-1 4G allele. Table 2 in the article reports that the observed change in (t-PA) activity in 4G/4G individuals who exercised was 0.38 ± 0.11. The article reports that this change is statistically significant because it has a p-value of less than 0.01. Therefore, the article provides further evidence that the specification recites stastically significant changes in (t-PA) activity in individuals carrying two copies of the PAI-1 4G allele who exercise. New claims 28 and 29 relate to this stastically significant change in (t-PA) activity after exercise when a person has two copies of the PAI-1 4G allele.

At pages 9-13, the Office Action further contends that the "specification does not provide any data concerning any sort of control group, for example a reference group that did not participate in an exercise program." Applicants respectfully disagree with this contention because the specification provides baseline data for the subjects examined, which represents t-PA activity and t-PA antigen levels prior to exercising. The baseline data was taken after the subjects completed the screening, dietary stabilization, and prior to commencing the exercise program. This is the control because it represents the (t-PA) activity and (t-PA) antigen levels of subjects consuming diet according to the experimental procedure and who have not exercised.

At pages 9-10, the Office Action further contends that there is no indication that improving fibrinolysis or alleviating symptoms of cardiovascular disease were measured. Directly measuring improved fibrinolysis or alleviating symptoms of cardiovascular disease is not necessary because, as the specification recites, there is a link connecting t-PA activity and t-PA antigen levels with improved fibrinolysis (see specification at paragraphs [0012], [0024] and [0050]). There is also a link connecting improved fibrinolysis with alleviated symptoms of cardiovascular disease (see specification at paragraphs [0003] and [0007]). According to MPEP §2107 (rev. 6 Sept. 2007), the Examiner must accept statements of fact made by the applicant as true. By accepting these facts as true, the specification provides data that fibrinolysis was improved and that symptoms of cardiovascular disease were alleviated in subjects with at least one 4G allele who engaged in exercise, because the specification establishes that increased (t-PA) activity or decreased (t-PA) antigen improves fibrinolysis, and thereby alleviates symptoms of cardiovascular disease.

Likewise, the specification also establishes that limited or extensive exercise will also improve fibrinolysis, and thereby, alleviate symptoms of cardiovascular disease. At paragraph [0050], the specification states that "endurance training, whether that training is extensive, moderate, or limited, increases fibrinolysis ....". Again, accepting this as true, which must be done in the absence of evidence to the contrary, the specification enables one skilled in the art to make and use the claimed invention with any level of exercise.

On page 10, the Office Action contends that the "specification does not provide any examples in which the genotype of a subject was identified at both the PAI-1 promoter and the t-PA gene locus". As discussed above, the amended claims are directed to identifying a person with at least one PAI-1 4G allele, and do not recite identifying a person having a t-PA I allele, therefore this rejection is moot.

For these reasons, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Conclusion

In view of the foregoing amendments to the claims and remarks, Applicants respectfully submit that the specification and claims are in condition for allowance. Accordingly, reconsideration and withdrawal of the asserted objections and rejections, and allowance of pending claims 1-18, 28 and 29, is respectfully requested. Rejoinder of withdrawn claims 21-27 is also requested.

Respectfully submitted,

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